AHRQ Healthcare Horizon Scanning System – Potential High-Impact Interventions Report

Priority Area 10: Obesity

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Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHSA290-2010-00006-C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual topic profiles are developed for technologies and programs that appear to be close to diffusion into practice in the United States. Those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify interventions that experts deemed, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually and topics included may change depending on expert comments received on interventions issued for comment during the preceding 6 months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in horizon scanning, assessing the leads for topics, or providing opinions regarding potential impact of interventions.

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None of the individuals compiling this information has any affiliations or financial involvement that conflicts with the material presented in this report.

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Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor emerging technologies and innovations in health care and to create an inventory of interventions that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption, except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the National Academy of Medicine (formerly the Institute of Medicine) and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is identifying and monitoring new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is analyzing the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future use and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High-Impact Interventions report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to: effectivehealthcare@ahrq.hhs.gov.

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Executive Summary

Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identification of new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 3 years out on the horizon and then to follow them up to 2 years after initial entry into the health care system. Since that implementation, review of more than 24,500 leads about potential topics has resulted in identification and tracking of about 2,400 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 750 topics are being actively tracked in the system.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice a year. Topics eligible for inclusion are those interventions expected to be within 0–3 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling information on topics and issuing topic drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 195 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest

(COIs). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the five to eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts' rationales are the main drivers for the designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of "lower," "moderate," or "higher" within the high-impact-potential range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received and as the development status of the interventions changes, the list of topics designated as having potentially high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ's Effective Health Care Web site.

Results

The table below lists the three topics for which (1) preliminary phase III data for drugs and phase II (or equivalent) data for devices and procedures were available; (2) information was compiled and sent for expert comment before November 6, 2015; and (3) we received six to eight sets of comments from experts between January 1, 2015, and November 16, 2015. (Ten topics in this priority area were being tracked in the system as of November 6, 2015.) We present two summaries on three topics that emerged as having high-impact potential on the basis of experts' comments and assessment of potential impact. The material on interventions in this Executive Summary and report is organized alphabetically. Readers are encouraged to read the detailed information on each intervention that follows the Executive Summary.

Priority Area 10: Obesity

Topic	High-Impact Potential
1. Liraglutide (Saxenda) for treatment of obesity	Moderately high
2. Orbera Intragastric Balloon System for treatment of obesity	Lower end of the high-impact-potential range
3. ReShape Integrated Dual Balloon System for treatment of obesity	Lower end of the high-impact-potential range

Discussion

According to a 2014 report from the National Center for Health Statistics (NCHS), 35% of adults (about 78.6 million) and 17% of youth (about 12.7 million) in the United States are obese (defined as an excess accumulation of body fat). Worldwide, obesity rates have more than doubled since 1980. According to the World Health Organization, in 2014, more than 1.9 billion adults aged 18 years or older (39%) were overweight; of these, more than 600 million (13%) were obese. Further, 42 million children younger than the age of 5 were overweight or obese in 2013.

According to NCHS, overweight adolescents have a 70% chance of becoming overweight adults. Non-Hispanic black adults have the highest age-adjusted rates of obesity (47.8% are obese), followed by rates for Hispanics (42.5%), non-Hispanic whites (32.6%), and non-Hispanic Asians (10.8%). Non-Hispanic black and Mexican-American men with higher incomes are more likely to be obese than non-Hispanic black and Mexican-American men with low incomes. Low-income

women are more likely to be obese than high-income women. Prevalence of obesity in adults has increased across all income and education levels. In children, obesity is higher among children living in low-income, low-education, and higher-unemployment households.

Obesity was at one time thought to be simply the result of caloric intake that exceeded energy expenditure. However, researchers now know that other factors including genetics, metabolism, behavior, environment, culture, and socioeconomic status contribute to obesity. Obesity is associated with increased risk of mortality and comorbidities, including type 2 diabetes mellitus (T2DM), coronary artery disease, dyslipidemia, cardiometabolic syndrome, hypertension, stroke, sleep apnea, osteoarthritis, gall bladder disease, and some cancers. In June 2013, the American Medical Association adopted a policy that recognizes obesity as a disease.

Body mass index (BMI), a measure of an individual's weight relative to his or her height (kg/m^2), is significantly correlated to an individual's body-fat percentage and is used as a measure to determine whether someone is overweight or obese. Individuals with a BMI of 25 kg/m^2 or higher are considered to be overweight, and those with a BMI of 30 kg/m^2 or higher are considered to be obese. Obesity is further classified as extreme or morbid in individuals with a BMI of 40 kg/m^2 or more.

Body fat distribution is also an important determinant of disease risk. Excess body fat in the abdominal area that is out of proportion to total body fat is known to be an independent predictor of morbidity and early mortality. Therapeutic intervention is considered to be urgently needed in men with a waist circumference greater than 40 inches and in women with a waist circumference greater than 35 inches.

The Healthcare Horizon Scanning System is tracking interventions in development for treating obesity including intragastric balloons, deep brain stimulation, a procedure to embolize certain abdominal arteries associated with production of appetite hormones, and drugs with reportedly new mechanisms of action and therapeutic targets.

Topics Deemed High-Impact

Intragastric Balloon Systems for Treatment of Obesity

- **Key Facts:** The Orbera™ Intragastric Balloon System is a temporarily placed single balloon intended to reduce weight without surgery by reducing the stomach's capacity to increase satiety with less food intake. To deploy the balloon, a physician uses an endoscope inserted through the patient's mouth to deploy the deflated balloon into the patient's stomach. The procedure takes 15- to 30-minutes and is performed with the patient under conscious sedation. When the device is properly positioned, the physician fills it with 400–700 cc saline. After 6 months, the physician removes the device in an endoscopic procedure similar to balloon placement. In August 2015, the U.S. Food and Drug Administration (FDA) approved Orbera for placement up to 6 months in conjunction with a long-term supervised diet and behavior modification program in adults with BMI of 30–40 kg/m^2 for whom more conservative weight measures have failed. A 1-year supervised weight-management program, which includes initial balloon implantation and planned retrieval 6 months later, reportedly costs between $6,000 and $8,000, including about $1,850 for the Orbera balloon. Most insurers do not cover intragastric balloon therapy for obesity, and patients have to pay out of pocket to receive the treatment. The U.S. Centers for Medicare & Medicaid Services (CMS) has a national coverage determination (established in 1987) denying coverage for intragastric balloons that stems from a first-generation intragastric balloon that was removed from the market due largely to adverse events and low efficacy.

In May 2015, Abu-Dayyeh and colleagues reported on weight loss achieved in 255 patients with BMIs of 30–40 kg/m^2 in the Orbera balloon's U.S. pivotal trial. At balloon removal, 71.8% of the balloon group achieved excess weight loss of 25% or more, compared with 31.9% in the control group. The Orbera group had 10.5%±6.6% mean total body weight loss compared with 4.7%±5.1% in the control group ($p<0.001$). At 26 weeks after balloon removal, 45.9% of the balloon group achieved excess weight loss of 25% or more, compared with 32.6% of the control group. The Orbera group had 7.7%±7.6% mean total body weight loss compared with 3.9%±6.1% in the control group ($p<0.001$). The balloon group showed greater improvement in eating behaviors and weight-related quality of life. Investigators observed no deaths or serious device-related adverse events.

The ReShape™ Integrated Dual Balloon System is a dual intragastric balloon system inserted during a procedure similar to that described for the Orbera balloon, except that two balloons are inserted endoscopically and each is filled with an equal volume of saline. Like the Orbera, the Reshape balloons are designed to be removed after 6 months. In July 2015, FDA approved the ReShape balloon for placement for up to 6 months in combination with a clinically supervised weight management program in adults with BMIs of 30–40 kg/m^2 who have been unable to lose weight through diet and exercise and who have at least one obesity-related comorbid condition, including diabetes, hypertension, or high cholesterol levels. The reported cost is similar to that for Orbera, including about $2,200 for the ReShape balloon. The same coverage conditions apply to both balloon systems.

In May 2015, Lopez-Nava and colleagues reported that patients in whom the ReShape balloon was implanted for at least 6 months experienced a mean total body weight loss of 15.4%, or 16.6 kg, corresponding to a 6.1-unit reduction in baseline BMI of 38.8 kg/m^2. Investigators observed no difference in total body weight loss between grade of obesity, age, or sex. However, severely obese patients were reported to have achieved greater total body weight loss, and women and less-obese subjects reportedly obtained higher percentages of excess weight loss.

- **Key Expert Comments:** Experts comments for both intragastric balloon systems were similar. Clinical experts thought the balloon systems may provide a less-invasive treatment option for patients with a BMI lower than that indicated for bariatric surgery and patients with a high BMI who may be candidates for bariatric surgery but are reluctant to undergo invasive surgery or who need to lose weight to become eligible for bariatric surgery. The likely lack of insurance coverage for intragastric balloons to treat obesity could make this treatment inaccessible to patients who cannot afford the out-of-pocket costs, potentially exacerbating health disparities, most experts anticipated. Some experts doubted the likelihood that most patients who undergo temporary placement of an intragastric balloon would be able to maintain achieved weight loss over the long term.
- **High-Impact Potential:** Lower end of the high-impact-potential range

Liraglutide (Saxenda) for Treatment of Obesity

- **Key Facts:** Liraglutide (Saxenda®) is a synthetic analogue of the peptide hormone glucagon-like peptide-1 (GLP-1), which is recognized for its ability to suppress appetite and energy intake, as well as delay gastric emptying (Astrup et al., 2009). The drug is believed to induce a feeling of satiety, which can result in lower caloric intake leading to weight reduction. Liraglutide is engineered to have a substantially longer half-life than endogenous GLP-1 (13 hours vs. 1–2 minutes). As an antiobesity treatment, liraglutide is self administered once daily via subcutaneous injection using an automatic injection pen with a recommended daily dose of 3 mg. In December 2014, FDA approved liraglutide for injection under the trade name Saxenda as a treatment for chronic weight management in addition to a reduced-calorie diet and physical activity. (Liraglutide was previously approved with a different brand name and dosage for treating diabetes.) Saxenda's labeling includes a boxed warning that highlights the possibility of thyroid tumors; this risk was identified in animal studies. The FDA approval required a risk evaluation and mitigation strategy to inform prescribers of potential risks with liraglutide use. Other approval conditions included multiple postmarketing studies to evaluate cardiovascular outcomes, potential risks of breast cancer and a form of thyroid cancer called medullary thyroid carcinoma, and liraglutide use in pediatric patients. As of November 2015, liraglutide reportedly cost about $1,075 to $1,175 at U.S. retail pharmacies for a 1-month supply at the recommended maintenance dose. Other weight-loss drugs (lorcaserin, naltrexone/bupropion, orlistat, phentermine/topiramate) reportedly cost between $195 and $570 for a 1-month supply. However, liraglutide may serve a dual purpose of treating diabetes in addition to reducing weight, so it may be an option for obese individuals with T2DM. In late November 2015, about 26 weeks after product launch, about 2,300 Saxenda prescriptions per week were reported to have been sold, up from 1,900 per week reported in mid-September 2015.
- **Key Expert Comments:** Experts generally thought that liraglutide has potential to fill an obesity treatment gap between highly invasive bariatric surgery and conservative measures. Although other obesity drugs are available, several experts cited liraglutide's potential to improve some measures of diabetes as complementing liraglutide's moderate potential for weight loss. Experts cited the cost, need for daily injections, and unknown long-term safety profile as potential barriers to wider acceptance from patients and physicians. Generally, experts did not expect liraglutide to substantially alter health care disparities or disrupt health care infrastructure or existing patient management procedures.
- **High-Impact Potential:** Moderately high

Obesity Interventions

Intragastric Balloon Systems for Treatment of Obesity

Unmet need: Bariatric surgery in the form of gastric bypass, sleeve gastrectomy, or laparoscopic banding is considered to be effective in many patients for treating obesity; however, some of these procedures are very invasive with serious risks and side effects, and some permanently alter the anatomy.[1] These procedures are indicated only for morbidly obese patients (body mass index [BMI] of more than 40 kg/m^2) or for obese patients with BMI of 35–40 kg/m^2 who have related comorbidities, such as type 2 diabetes mellitus (T2DM).[2] However, a treatment gap exists between invasive bariatric surgery and more conservative measures, such as diet, exercise, and pharmacotherapy, for patients with less severe obesity. Minimally invasive treatments are needed that could enable these patients to lose weight when conservative measures are unsuccessful and to slow or prevent progression to extreme obesity.[3,4] Two temporary intragastric balloon systems that were recently approved by the U.S. Food and Drug Administration (FDA) for treating obesity are discussed below.

Intervention: The Orbera™ Intragastric Balloon System is an expandable silicone balloon that is temporarily placed in the stomach without altering gastric anatomy with the goal of promoting greater satiety with less food intake and increasing weight loss in individuals who are obese.[5] To deploy the balloon, a physician inserts the deflated Orbera balloon into the patient's stomach using an endoscope inserted through the mouth to perform and guide the 15- to 30-minute outpatient procedure with the patient under conscious sedation. When the balloon is appropriately positioned, the physician fills it with 400–700 cc saline and detaches the deployment catheter's filling tube, which closes the balloon's self-sealing valve. The saline contains methylene blue dye that alters urine color to alert patients about a device problem requiring medical attention in the event of a balloon leak or rupture.[6-8] After 6 months, a physician removes the Orbera balloon using an endoscopic outpatient procedure similar to that used during balloon placement. With the patient under conscious sedation, the physician advances the endoscope through the patient's mouth and into the stomach to drain the saline, after which the deflated balloon is endoscopically captured for removal.[6,8,9]

The ReShape Integrated Dual Balloon System differs slightly from the Orbera in that it uses two temporarily placed intragastric balloons.[10] The procedure is performed similarly and takes the same amount of time as the Orbera balloon placement. The two balloons, once placed, are inflated each in turn with equal volumes of saline (450 cc each). The saline contains methylene blue dye that alters urine color to alert patients about a device problem requiring medical attention, in the event of a balloon leak or rupture.[10,11] Compared with single intragastric balloons, the dual-balloon design purportedly allows for a greater volume of the stomach to be occupied.[10,12]

The ReShape balloons are designed to be removed 6 months after placement using an endoscopic procedure similar to the balloon placement. During this procedure, the endoscope is fitted with a proprietary suction cap to drain the saline from the balloons individually in a controlled manner. Once the balloons are drained, the clinician secures the deflated dual balloon's tip with a snare on the endoscope and removes the device through the patient's mouth.[10]

Clinical trials Orbera: In May 2015, Abu-Dayyeh and colleagues reported on weight loss achieved in 255 patients, aged 18–65 years, with BMIs of 30–40 kg/m^2, enrolled in the U.S. pivotal trial of the Orbera intragastric balloon.[13] Subjects were randomly assigned either to receive Orbera balloon placement and to participate in a behavioral management program (BMP) or to participate in the BMP alone. Primary endpoints were percentage change of excess weight loss (EWL) and percentage change of total body weight loss (TBWL).

Overall, 78.4% (98 of 125) of the balloon group and 71.5% (93 of 130) of the BMP-only group completed the 52 weeks of the study. At 26 weeks (balloon removal), 71.8% of the balloon group achieved 25% or more EWL, compared with 31.9% in the BMP-only group. The balloon group had 10.5%±6.6% mean TBWL, compared with 4.7%±5.1% in the BMP-only group ($p<0.001$ on an intention to treat [ITT] analysis). At 52 weeks (26 weeks after balloon removal), 45.9% of the balloon group achieved 25% or more EWL, compared with 32.6% of the BMP-only group. The balloon group had 7.7%±7.6% mean TBWL, compared with 3.9%±6.1% in the BMP-only group ($p<0.001$ on ITT analysis). Furthermore, 43% (95% confidence interval, 33% to 53.3%) of balloon patients experienced EWL that was above the mean change in EWL of BMP-only patients by 15% or more at 52 weeks. Both groups had a decrease in the severity of comorbid diabetes, hypertension, and dyslipidemia from baseline. The balloon group showed greater improvements in eating behaviors and weight-related quality of life. Investigators observed no deaths or serious device-related adverse events.[13]

In April 2015, Fittipaldi-Fernandez and colleagues reported on 2,727 patients in Brazil with BMIs of 27 kg/m^2 or greater who underwent Orbera balloon placement plus multidisciplinary team followup from a nutritionist, psychologist, and physician.[14] Investigators categorized patients as overweight or obese, further classified as grade I, II, or III obesity, without specifying thresholds for each subgroup. Overall, 188 patients were excluded from the analysis. Reasons for exclusion were as follows: early balloon removal (114 patients, 4.18%), absence of weight loss or weight gain (27 patients, 0.99%), incomplete data (9 patients, 0.33%), contamination of balloon contents (6 patients, 0.22%), balloon leakage (15 patients, 0.55%), pregnancy (9 patients, 0.33%), balloon removal from other teams' patients (3 patients, 0.11%), and at 1 patient (0.03%) each, Wernick Korsakoff syndrome due to excessive vomiting, pancreatitis, early removal due to a need for oral nonsteroidal anti-inflammatory drugs, gastric perforation, and upper digestive bleeding.

Of the 2,539 remaining patients, mean age was 37.56 years; 1,908 were women and 631 were men. Patients experienced significant weight loss from treatment. Baseline BMI changed from a mean of 36.23±5.70 kg/m^2 (range: 27–74.74) to a mean of 28.91±7.83 kg/m^2 (range: 18.98–58.00) after treatment ($p<0.0001$). Mean BMI reduction was 7.38±3.99 kg/m^2 (range: 0.25–29.79). Mean percent TBWL was 20.09%±7.61% and mean percentage EWL (%EWL) was 74.23% ±36.71% (range: 3.99%–336.14%[*sic*]). The treatment success rate, defined as %EWL of more than 25%, was 94.7%. Percentage EWL was highest in the overweight group at 147% EWL, followed by obesity grade I at 82.91%, grade II at 62.12%, and grade III at 51.44%, ($p<0.0001$). Women achieved 76.31% EWL compared with 68.08% EWL in men ($p<0.0001$).[14]

Clinical Trials ReShape: In May 2015, Lopez-Nava and colleagues reported on TBWL, percentage of baseline TBWL (%TBWL), percentage of EWL (%EWL), and adverse events in 60 patients who received a ReShape dual balloon.[15] Patients had balloons in place for at least 6 months and also received regular counseling from a multidisciplinary team. Investigators reported that initial BMI of 38.8 kg/m^2 decreased by 6.1 units, with the following mean results: 16.6 kg TBWL, 15.4% TBWL, and 47.1% EWL. Investigators observed no difference in %TBWL between grade of obesity, age, or sex. However, morbidly obese patients were reported to have achieved greater TBWL, and women and less-obese subjects reportedly obtained higher %EWL. Patients were reported to have generally tolerated the balloon well, with one early removal for patient intolerance, one early deflation without migration, and one gastric perforation. Fourteen patients were reported to have developed small, clinically insignificant ulcers or erosions noted at the time of balloon retrieval.[15]

In December 2014, Ponce and colleagues reported on %EWL and ReShape balloon treatment responder rate among 326 patients with BMIs of 30–40 kg/m^2 who were randomly assigned to endoscopic ReShape treatment plus diet and exercise (ReShape, n=187) or sham endoscopy plus

diet and exercise (n=139) for 24 weeks.[16] Both primary endpoints were met in the study. The ReShape group was reported to have achieved significantly greater %EWL at 24 weeks (25.1% ITT, 27.9% completed cases [CC, n=167]) than the sham endoscopy group (11.3% ITT, p=0.004, 12.3% CC, n=126). Investigators found that the ReShape group significantly exceeded a prespecified 35% response rate (49.1% ITT, p<0.001, 54.5% CC) for weight loss dichotomized at 25% EWL. Accommodative symptoms abated rapidly with support and medication. Balloon deflation without migration occurred in 6% of the ReShape group. Investigators retrieved the device early for nonulcer intolerance in 9% of patients. Gastric ulcers occurred in 10% of the ReShape group. Investigators noted that a minor device change significantly reduced the size and frequency of ulcers.[16]

Manufacturer and regulatory status: Apollo Endosurgery, Inc. (Austin, TX), manufactures the Orbera Intragastric Balloon System. In August 2015, FDA approved Orbera as an adjunct to weight reduction in adults with BMI of 30–40 kg/m^2 for whom more conservative weight reduction alternatives, such as supervised diet, exercise, and behavior modification programs, have failed.[17] The device is intended for placement for up to 6 months and is to be used in conjunction with a long-term supervised diet and behavior modification program designed to increase the possibility of significant long-term weight loss and maintenance of that weight loss.[7]

ReShape Medical, Inc. (San Clemente, CA), manufactures the ReShape Integrated Dual Balloon System. In July 2015, FDA approved the ReShape balloon without requiring an FDA advisory panel meeting.[18,19] The device is indicated for placement for up to 6 months in adults with BMIs of 30–40 kg/m^2 who have been unable to lose weight through diet and exercise and who have at least one obesity-related comorbid condition, including diabetes, hypertension, or high cholesterol levels. Patients in whom the ReShape dual balloon is implanted should also participate in a structured diet, exercise, and health-coaching program under a health care provider's supervision.[11,18,19]

Diffusion: The Orbera and ReShape balloons compete with each other. As of November 2015, manufacturers had not reported sales of either of the balloons. Moderate diffusion could be expected in the eligible obese population as an adjunct to lifestyle modifications. According to the manufacturer, Orbera balloons have been commercially available in international markets for more than 20 years and are distributed in more than 80 countries worldwide.[17] Another competitor, the Obalon intragastric balloon, is in late-phase development for the U.S. market.[20]

The experience with other intragastric balloons might influence perceptions of these new intragastric balloons. An early generation, single intragastric balloon (Garren-Edwards Gastric Bubble, American Edwards Laboratories [now part of Edwards Lifesciences, Irvine, CA]) was introduced in 1985 and withdrawn from the U.S. market in 1992 because of concerns about safety and efficacy, because of frequent complications.[21] A 2007 review by the Cochrane Metabolic and Endocrine Disorders Group concluded that "Compared with conventional management, IGB [intragastric balloons] did not show convincing evidence of a greater weight loss. The relative risks for minor complications, for example gastric ulcers and erosions were significantly raised."[22] In 1987, the U.S. Centers for Medicare & Medicaid Services (CMS) established a national coverage determination (NCD) regarding gastric balloons. The NCD indicated that "the use of the gastric balloon is not covered under Medicare, since the long term safety and efficacy of the device in the treatment of obesity has not been established."[23] A subsequent NCD for bariatric surgery for treating morbid obesity issued in 2013 notes that CMS's previous noncoverage policy for intragastric balloons for obesity remains unchanged and in force.[24] Because of this NCD, intragastric balloons coming to the U.S. market would have to undergo a new formal national coverage analysis to establish coverage under Medicare. If Medicare were to cover the balloons, other third-party payers might follow suit.

According to ECRI Institute's PriceGuide Database, the average price paid for the Orbera intragastric balloon in the United States as reported by several member hospitals was $1,850 (this does not include placement costs, patient followup, or device removal).[25] According to ECRI Institute's PriceGuide Database, the average price paid for the ReShape intragastric balloon in the United States as reported by member hospitals is $2,200 (also not including placement costs, patient followup, or device removal).[26] Early adopters of these balloons at some U.S. obesity programs have reported that a 1-year supervised weight-management program, which includes initial balloon implantation and planned retrieval 6 months later, costs patients between $6,000 and $8,000 and that most insurers do not cover intragastric balloon therapy.[27,28] Estimated costs for intragastric balloon placement in the United Kingdom are reportedly about £4,450 ($6,809 as of November 2015).[29,30] In Canada, the fee for an intragastric balloon and placement procedure is reported to be about $8,000. This fee includes balloon insertion and removal, followup visits, and nutrition and dietitian support services.[21] Diffusion is likely to be hampered if payers choose not to reimburse for its use.

A search of 11 representative, private, third-party payers that publish their coverage policies online found no payers that cover use of intragastric balloons to treat obesity. Payers that consider intragastric balloons to treat obesity to be investigational or experimental and specifically deny coverage include Aetna,[31] Anthem,[32] CIGNA,[33] HealthPartners,[34] Humana,[35] Medica,[36] and UnitedHealthcare.[37]

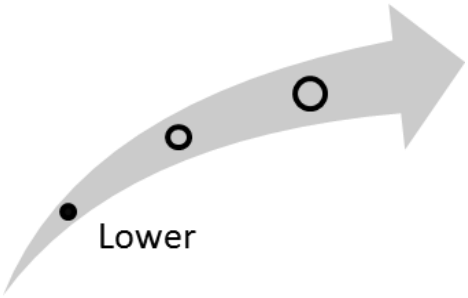
For patients with BMIs between 30 and 40 kg/m^2, the balloons could compete with approved pharmacotherapies for obesity (i.e., liraglutide, lorcaserin, naltrexone/bupropion, phentermine/topiramate).

Weight-loss surgery is indicated for patients only after other therapies have failed or in cases in which patients are experiencing complications related to their obesity.[38] Therefore, the balloons will likely compete with these surgeries only in patients with BMIs of 35 kg/m^2 or more and obesity-related comorbidities. Intragastric balloons may also compete with other endoluminal treatments that are more invasive but also reversible, such as the VBLOC Maestro® vagus nerve blocking system.[39]

Clinical Pathway at Point of This Intervention

The National Heart, Lung and Blood Institute's Panel on Weight Loss recommends that patients who are morbidly obese lose 10% of their excess body weight before bariatric surgery to help reduce both surgical risks and postoperative complications. Losing weight through diet and exercise alone has often been unsuccessful in this patient population. Therefore, physicians may also recommend weight-loss medication.[40] If goals are not achieved with medications, patients may opt for new, minimally invasive options, such as intragastric balloons. The Orbera and ReShape Duo balloon devices are indicated for placement for up to 6 months in combination with a supervised diet and behavior modification program designed to increase the possibility of significant long-term weight loss and maintenance of that weight loss.[7,11,17-19]

Figure 1. Overall high-impact potential: intragastric balloon systems for treatment of obesity



Experts generally regarded the intragastric balloons as having moderate short-term potential to fulfill a large unmet need for effective new obesity treatments that are less invasive than bariatric surgery. Experts noted the balloons' relative safety and efficacy in reducing weight based on available trial data. However, experts also cited the possibility of weight regain after temporary balloon placement as limiting its long-term potential health benefit. Additionally, the likely lack of insurance coverage coupled with the estimated $6,000 to $8,000 for balloon implantation and retrieval plus a clinically supervised weight management program could reduce patient acceptance and access to treatment. Experience with a first-generation intragastric balloon that has since been removed from the market may also affect acceptance from some clinicians. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, provided perspectives on the Orbera balloon[41-46] and six experts, with similar backgrounds, provided perspectives on the ReShape balloons.[47-52] Most of the experts' comments were similar for both balloon systems. We have organized the following discussion of expert comments by the parameters on which they commented.

Unmet need and health outcomes: Most experts recognized a moderate to large unmet need for obesity treatment alternatives—as demonstrated by the growing obese population and often modest efficacy of diet and exercise—between conservative measures and invasive bariatric surgery and weight-loss drugs. Based on available data, the Orbera balloon appears to have moderate potential to improve patient health, the majority of experts concluded. One expert with a clinical background noted that the Orbera balloon may be an important new option for patients in the lower-BMI range, stating, "Given the eligibility of low BMI patients for treatment, it may be possible, particularly for the 30-34.99 group, to possibly delay or prevent the development or progression of obesity if patients can focus on long term maintenance strategies once the device is explanted. Otherwise, it can be used as a bridge to other definitive procedures, risk mitigation, [or] bridge to other non-bariatric surgeries that limit BMI, such as organ transplant."[46] However, experts differed in their confidence that the Orbera balloon could effectively fill the unmet need for new, less-invasive obesity treatments. Four experts with clinical and research backgrounds were more optimistic that the balloon could fill the unmet need.[41,42,44,46] One clinical expert noted, "If larger studies determine the Orbera Intragastric Balloon System is effective and safe, this procedure could potentially emerge as a major short-term therapy for obesity."[41] Another clinical expert characterized those patients with BMI between 30 and 40 who would not be indicated for or who would not desire bariatric surgery as "a huge number of patients that could benefit from this intervention." This clinical expert continued, "Endoscopic treatments are generally much more accepted by patients than any surgical treatment, and even possibly [preferable] to daily

consumption of medications."[46] However, two experts with health systems and research backgrounds doubted the Orbera balloon's ability to fill the unmet need.[43,45] The health systems expert stated, "It is hard for me to believe that the majority of morbidly obese patients will have long-term benefit from this treatment and will most likely not maintain the needed regimen of diet and exercise to continue to lose…weight" and maintain that weight loss.[45] One research expert cited the existing Medicare noncoverage policy for intragastric balloons and the availability of another FDA-approved intragastric balloon (i.e., ReShape device) as limiting the Orbera balloon's potential to fill the unmet need.[43]

Most experts acknowledged a large unmet need for less-invasive interventions to bariatric surgery that the ReShape balloon is intended to fill. "Currently there is a large gap for the largest group of patients [with] BMI 30–34.9, and BMI 35–39.9 who do not have serious obesity comorbid conditions, who are amenable only to treatments that currently include medications, the laparoscopic adjustable gastric band and/or ongoing dietary and lifestyle modification," stated one clinical expert.[48] Another clinical expert observed, "Obesity affects more than 35% of adults in the U.S. and increases the risk of developing type 2 diabetes, atherosclerosis, non-alcoholic fatty liver disease, and other diseases. Diet and exercise and currently available medications are ineffective in long-term weight loss. Although gastric bypass surgery and sleeve gastrectomy are effective, these procedures are not practical in large populations of obese patients, and less than 1% of eligible patients choose to undergo bariatric surgery. Therefore, there is an unmet need for alternative therapies for obesity."[50] However, two experts with health systems and research backgrounds disagreed. One research expert observed that available data on lifestyle modification and weight-loss drugs suggest that many patients will regain the weight lost during intervention and may even gain additional weight (compared with starting weight).[51] "Although treatment of obesity is a very important unmet need, I would say temporary treatment of obesity (6 months to maybe 1.5 years time frame) is not a very important unmet need," this research expert stated.[51] Available clinical data suggest the ReShape balloon has good potential for short-term weight loss with reasonable safety, the majority of experts noted. However, two experts with clinical and research backgrounds expressed concerns that the short-term weight loss benefit would persist. One clinical expert opined, "Although weight loss outcomes appear at 6 months to be better than that for all medication trials, short-term tolerance is a concern for some, but more importantly there is lack of long-term data to show any form of durable weight loss and like any other short term treatment, there is a concern regarding overall efficacy given the risk of weight regain."[48] A research expert stated, "No research looks at if this weight loss is maintained and whether it has an effect on long term outcomes. I suspect the weight loss is temporary and doesn't have an effect on long term outcomes. Additionally, at some point research was done indicating the yo yo dieting (which this effectively is) is harmful to your health. I'm not sure if that was ever debunked, but it may be a factor here."[51] Experts were divided on the ReShape balloon's potential to fill the unmet need. One research expert stated, "The ReShape Integrated Balloon System has great potential to address the issue of obesity and weight loss in the intended patient population. There are some risks involved in the intervention, but studies so far indicate that the treatment is effective. More completed studies would likely help solidify this. Use of the balloon is very dependent on a patient's situation, but may be a good alternative to surgery, or even as a pre-surgery intervention. After training, clinicians may find the insertion and removal procedures to be simpler than an alternative like surgery, as well."[52] Likewise, a clinical expert noted, "The Reshape Integrated Dual Balloon System has the potential to expand treatment choices, and serve at a means of initiating weight loss followed by long-term intensive dietary and behavioral intervention. The Reshape Integrated Dual Balloon System is less invasive and technically feasible in most obese patients."[50] Other experts were less sure of its potential to fill the unmet need. "Overall, the device is an alternative to many patients

who cannot qualify for standard bariatric procedures and may be a bridge for others that could not obtain a separate type of procedure [such as organ transplant] that in some cases may be time-sensitive and potentially life-threatening. It is however, a questionable application, given the short duration of implantation. It is expensive and will not be covered by insurance initially or possibly ever, limiting the number of individuals that would likely seek this treatment," a clinical expert suggested.[48]

Acceptance and adoption: The balloons would likely see moderate adoption, with patient acceptance likely being greater than physician adoption, the experts generally agreed. "These patients are essentially out of options. If they truly want to lose weight, it seems to be a reasonable solution," one health systems expert opined.[45] One clinical expert noted, "Patients are likely to accept the Orbera system because current medical therapies for obesity are ineffective, and most patients eligible for bariatric surgery have concerns about intraoperative and long-term safety."[41] "The [ReShape] device is safe, with short term efficacy above that of medications. It will likely be perceived well by most physicians who do not medically manage obesity, but would likely refer their patients for either medical or surgical obesity treatment," one clinical expert noted.[48] One clinical expert observed, "Patients generally prefer any type of endoscopic procedure to a procedure involving incisions. It will be perceived by patients as much safer and with less risk as there is no permanent alteration of the gastrointestinal tract or incisional pain."[48] A research expert stated, "Even though this treatment is unlikely to produce long-term results, I think patients will be more accepting of it than clinicians. First of all, it represents an 'easy' path to weight loss. Patients can eat normally (although they will hopefully modify their diet) and still lose weight. Also, it has less serious side effects than surgery. It also appeals to vanity because a considerable proportion of patients will lose weight in a relatively short amount of time using this treatment. One could even speculate patients seeking out this treatment before a significant event."[51]

All experts agreed that the estimated $6,000 to $8,000 cost to patients and likely lack of insurance coverage for balloon implantation and weight loss management programs would have a small financial effect on the health care system but could impact patients greatly and limit patient acceptance, although patient interest in the procedure would likely remain fairly strong. Overall, experts anticipated moderate physician acceptance for the balloons. Some experts thought the need to learn a new procedure and unfavorable experience with first-generation balloons might reduce its appeal to some clinicians, although many clinicians would still welcome the new treatment option.[42-44] The two clinical experts expected good acceptance from health care providers.[41,46] One noted, "It may be quicker and easier to perform this procedure over stapled bariatric procedures with less risk of post-procedural complications that require emergent intervention."[46] Further, this clinical expert suspected that Orbera implantation may provide clinicians a "cost incentive" because the balloon procedure's effective reimbursement rate from cash-paying patients may be greater than the reimbursement rate for stapled bariatric procedures that insurance companies may cover.[46]

Health care delivery infrastructure and patient management: Overall, experts did not anticipate the intragastric balloon procedures would create substantial disruptions to health care infrastructure or patient management at centers with established programs that provide comprehensive weight management and bariatric surgery. One clinical expert acknowledged a somewhat larger change to patient management with the balloon, stating, "Currently weight management is evaluated medically or surgically or a combination of both, but does not generally involve GI [gastrointestinal] physicians, who may not also have an ongoing weight management program, such as access to behavioral providers and dietitians, which may be beneficial for further ongoing weight loss and for maintenance after retrieval."[46] In contrast, one research expert disagreed, stating, "This is definitely a different type of device" that would require changes in

infrastructure and clinician training regarding patient indications and post-implantation management strategies.[44]

"In implementing this intervention [ReShape], some patients may be able to avoid more serious procedures like surgery and replace it with a 15- to 30-minute outpatient procedure," stated one research expert, going on to note, "However, when comparing to pharmacotherapy as another intervention step, there is not much difference in terms of patient management. Both the balloon and pharmacotherapy require some level of monitoring throughout the treatment. The change in the way a patient would be managed is very dependent on the current situation, such as whether or not they are candidates for the surgery option."[52] However, another research expert stated, "This is definitely a different type of device" that would require changes in infrastructure and clinician training regarding patient indications and post-implantation management strategies.[47] Potential disruptions may depend on the type of health care provider. One clinical expert suggested potential changes for certain providers, noting "This device is being placed already and will likely continue to [be] by gastroenterologists–historically, somewhat out of the loop of weight management…. It is unclear whether the GI physicians will provide the overall optimal infrastructure [e.g., lifestyle coaching and ongoing support] for these patients and this would involve an investment and change for these providers."[48]

Health disparities: Experts generally believed the intragastric balloons have moderate potential to affect health disparities, but they diverged on whether the balloon devices would likely reduce or increase disparities. One clinical expert stated, "Obesity rates are higher among low socioeconomic groups, African Americans, Hispanics, and Native Americans. These populations are typically underserved and have limited resources for intensive dietary, behavioral and other therapies needed for obesity management. These groups are also less likely to accept invasive bariatric procedures partly due to fears about long-term complications, socio-cultural factors, and high operative and long-term costs. The balloon has the potential to reduce health disparities because it is less invasive, has lower short-term costs, and can be used to augment medically-induced weight loss."[41] However, another clinical expert opined, "This device is unlikely to be covered by insurance, and therefore will only likely be a cash pay option for most patients and have little impact on reducing health disparities."[46] A research expert concurred, describing the balloons as a "fancy new device unlikely to be accessible to everyone, and so disparities could exacerbate."[44]

The estimated $6,000 to $8,000 for balloon therapy and the required year-long supervised weight management program would remain financially out of reach for many lower-income patients who may be more affected by obesity, experts concurred. These sentiments were exemplified by a clinical expert who remarked, "The device is unlikely to be covered by third-party payers at this time, and therefore, there is a real cost to the patient. Although less than other cash pay bariatric options or the laparoscopic adjustable gastric band, it will only likely be an option for patients who could afford the out of pocket costs and therefore will not have any impact on reducing health disparities."[48]

Liraglutide (Saxenda) for Treatment of Obesity

Unmet need: The increasing prevalence of overweight and obese populations in the United States has generated a need for novel pharmacologic therapies aimed at weight reduction when diet and exercise have failed. However, concerns about potential adverse events associated with antiobesity pharmacotherapies significantly elevated the FDA's regulatory bar for gaining approval, with developers required to provide long-term safety data with new drug applications and commit to long-term postmarket studies.[53-56] FDA approved three antiobesity drugs—phentermine/topiramate, lorcaserin, and naltrexone/bupropion—between 2012 and the end of 2014.[55-58] These drugs may not provide dramatic weight loss for many patients, more effective pharmacotherapies are needed.

Intervention: Liraglutide is a synthetic analogue of the peptide hormone glucagon-like peptide-1 (GLP-1) that has been shown to suppress appetite and energy intake and delay gastric emptying, which may induce a feeling of satiety.[59] GLP-1 is a naturally occurring incretin hormone that stimulates insulin production in the presence of hyperglycemia and blocks the effects of glucagon, a hormone produced in the pancreas that signals the liver to release stored sugar into the bloodstream.[60] Endogenous human GLP-1 has a short half-life (1–2 minutes); however, liraglutide has been modified to allow binding to serum albumin, which increases its half-life to about 13 hours. The drug was previously approved by FDA to treat T2DM by stimulating insulin release and lowering glucagon secretion in response to high blood glucose levels.[59]

As an antiobesity treatment, liraglutide is self-administered, once daily, by subcutaneous injection using an automatic pen injector; the recommended daily dose is 3 mg, which is roughly twice the dose used for treating T2DM[61] (1.2–1.8 mg daily).[62] In practice, given that many patients with diabetes are also obese, the drug may fulfill a dual role of managing both diabetes and obesity. Nonetheless, the manufacturer pursued separate labeled indications for treating overweight and obesity.[63]

Clinical trials: In July 2015, Pi-Sunyer and colleagues reported on comparative weight loss in 3,731 patients in the phase III, randomized controlled SCALE™ trial.[64] The trial randomly assigned patients without diabetes who were overweight (BMI of 27 kg/m^2 or greater with treated or untreated dyslipidemia or hypertension) or obese (BMI of 30 kg/m^2 or greater) to receive once-daily 3 mg liraglutide (n=2,487) or placebo (n=1,244) injections plus diet and exercise for 56 weeks. At baseline, patients had a mean (±SD) age of 45.1±12.0 years, mean weight of 106.2±21.4 kg, and a mean BMI of 38.3±6.4. Overall, 78.5% of patients were women and 61.2% had prediabetes. Liraglutide group patients lost a mean of 8.4±7.3 kg compared with 2.8±6.5 kg in the placebo group (treatment difference of -5.6 kg; 95% confidence interval, -6.0 to -5.1; $p<0.001$). Weight loss of at least 5% body weight was achieved in 63.2% of liraglutide patients compared with 27.1% of placebo patients ($p<0.001$). Weight loss of at least 10% was reached by 33.1% of liraglutide patients and 10.6% of placebo patients ($p<0.001$).[64]

In March 2015, Wilding and colleagues reported other outcomes for the same patient groups in the SCALE – Obesity and Pre-diabetes trial.[65,66] Mild to moderate nausea and diarrhea were the most common adverse events in the liraglutide group. Incidence of serious adverse events was not statistically different: 6.3% in the liraglutide group and 5.0% in the placebo group. Liraglutide use showed higher incidence than placebo for gallbladder-related adverse events (3.1 vs. 1.4 events per patient-year of exposure) and acute pancreatitis (0.4 vs. <0.1 events per 100 patient-years at risk). The study also showed increased lipase activity with liraglutide use, but most elevations were transient and not predictive of pancreatitis. Liraglutide reduced mean systolic and diastolic blood pressure versus placebo (estimated treatment difference [ETD] -2.8 and -0.9 mm Hg; $p<0.001$) but increased mean pulse (ETD 2.4 beats/minute; $p<0.0001$). Cardiovascular events were not

statistically different between liraglutide and placebo groups (8.7% vs. 9.9%, respectively). Investigators noted that the safety profile of liraglutide 3 mg injection was consistent with known effects of GLP-1 receptor agonists. The drug was not associated with increased risk of depression or suicidal thoughts.[65] Investigators also reported that liraglutide injection improved fasting and post-load glycemia level compared with placebo (ETD: fasting plasma glucose -0.38 mmol/L, plasma glucose [oral glucose tolerance test, area under the curve] -2.0 mmol/L, glycated hemoglobin [HbA_{1c}] -0.23%; $p<0.0001$ for all). More individuals with prediabetes had reverted to normal glycemic levels on liraglutide 3 mg than on placebo (69.7% vs. 32.1%; $p<0.0001$), while more individuals with normal glycemic levels had progressed to prediabetes on placebo than on liraglutide (19.9% vs. 6.9%; $p<0.0001$). Further, more individuals taking placebo developed T2DM than individuals taking liraglutide (14 vs. 4 individuals; $p=0.0003$).[66]

Manufacturer and regulatory status: Novo Nordisk a/s (Bagsvaerd, Denmark) manufactures liraglutide. In December 2014, FDA approved the drug under the trade name Saxenda® for chronic weight management in addition to a reduced-calorie diet and physical activity.[67]

According to FDA, Saxenda's labeling has a boxed warning that highlights rodent studies linking liraglutide to C-cell tumors of the thyroid gland. However, no link between liraglutide and thyroid C-cell tumors, including a thyroid cancer called medullary thyroid carcinoma (MTC), has been identified in humans. FDA advises that liraglutide should not be used in patients with a personal or family history of MTC or in patients with multiple endocrine neoplasia syndrome type 2 (a disease in which patients have tumors in more than 1 gland in their body, which predisposes them to MTC).[67] FDA required a risk evaluation and mitigation strategy for approval to inform prescribers of potential risks from liraglutide use.

The company must also conduct multiple postmarketing studies for liraglutide: trials to evaluate dosing, safety, and efficacy in pediatric patients; an animal study to evaluate potential effects on growth, sexual maturation, and central nervous system development and function; an MTC case registry of at least 15 years duration to identify any increase in MTC incidence; and an evaluation of the potential risk of breast cancer in ongoing clinical trials. The company is also conducting a cardiovascular outcomes trial.[67,68]

FDA approved liraglutide injection in January 2010 under the trade name Victoza® as an adjunct to diet and exercise to improve glycemic control in adults with T2DM.[69] In January 2015, liraglutide received approval from the European Commission for weight management in overweight or obese adults in addition to a reduced-calorie diet and physical activity.[70]

Diffusion: Since liraglutide received FDA approval to treat obesity in December 2014, Novo Nordisk has announced plans to assign about 500 of its 3,000 U.S. sales representatives to heavily promote Saxenda for obesity treatment in the United States.[71] The company reportedly anticipates reaching "blockbuster" status for the drug with $1 billion or more in annual sales worldwide, despite other competitors in the obesity drug market.[71,72] In October 2015, Novo Nordisk reported that liraglutide was increasingly being added to formularies of U.S. health plans, and that 50 million covered lives had formulary access to the drug.[73] Analyst reports citing IMS statistics on prescriptions written indicate that in late November 2015, about 26 weeks after product launch, about 2,300 Saxenda prescriptions per week were reported to have been sold, up from 1,900 per week reported in September 2015.[74]

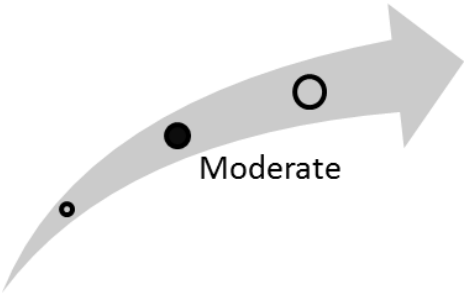
As of November 2015, liraglutide reportedly cost about $1,075 to $1,175 at U.S. retail pharmacies for a 1-month supply (five 3 mL pens at a dose of 3.0 mg/0.5 mL) at the recommended maintenance dose.[75,76] Novo Nordisk offers a patient assistance program to help defray costs of copayments for patients with insurance and to purchase the drug for patients without insurance.[77] Competing weight-loss drugs (lorcaserin, naltrexone/bupropion, orlistat, phentermine/topiramate) reportedly cost between $195 and $570 for a 1-month supply.[78-81]

We searched 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield of Alabama, Blue Cross/Blue Shield of Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) to identify policies that mention Saxenda or liraglutide injection for treating obesity. Depending on plan language, Aetna may cover liraglutide (Saxenda) for obesity when selection criteria are met; however, "many Aetna plan benefit descriptions specifically exclude services and supplies for or related to treatment of obesity or for diet and weight control."[82] CIGNA requires prior authorization for Saxenda prescriptions for obesity.[83] Medica considers Saxenda a tier 3 drug with step-therapy requirements.[84]

Clinical Pathway at Point of This Intervention

Endocrine Society clinical guidelines on using pharmacology to manage obesity suggest using FDA-approved weight-loss medications (over no medication therapy) to improve comorbidities and adherence to behavior changes, which they state may improve physical functioning and enable more physical activity in individuals with BMIs of 30 kg/m^2 or more or in individuals with BMIs of 27 kg/m^2 or more and at least one obesity-related comorbid condition.[85] The guidelines further recommend that clinicians monitor obesity drug safety and efficacy at least monthly for the first 3 months, then at least every 3 months in all patients prescribed weight-loss medications. If clinicians determine drug therapy is safe and effective, defined as weight loss of 5% or greater of body weight at 3 months, the guidelines recommend continuing the medication, and stopping if ineffective or unsafe.[85] Further, the Endocrine Society guidelines state, "In patients with T2DM who are overweight or obese, we suggest the use of antidiabetic medications that have additional actions to promote weight loss (such as glucagon-like peptide-1 [GLP-1] analogs or sodium-glucose-linked transporter-2 [SGLT-2] inhibitors), in addition to the first-line agent for T2DM and obesity, metformin."[85] Thus, liraglutide injection would be used as adjunctive therapy to diet and lifestyle and behavior modification for patients with obesity.

Figure 2. Overall high-impact potential: liraglutide (Saxenda) for treatment of obesity



Overall, experts thought that liraglutide has potential to fulfill an unmet need for new alternatives to invasive bariatric surgery. Several experts noted that the moderate weight loss that liraglutide offers would be complemented by the potential to improve some measures of T2DM. Experts cited the cost, need for daily injections, and unknown long-term safety profile as potential barriers to wider acceptance from patients and physicians. Generally, experts did not expect liraglutide use to substantially alter health care disparities or disrupt health care infrastructure or existing patient management procedures. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems perspectives, offered perspectives on liraglutide.[86-91] One clinical expert reported consulting relationships with other manufacturers of antiobesity medical devices.[86] This conflict of interest is balanced by views of the other experts, who reported no potential conflict of interest. We have organized the following discussion of expert comments by the parameters on which they commented.

Unmet need and health outcomes: Most experts cited a moderate to large unmet need for new obesity treatments, especially pharmacotherapies, that could be options in a treatment continuum between invasive bariatric surgery and diet and lifestyle modifications to improve patient outcomes and address the needs of an increasing population with obesity and comorbid conditions.[86,87,89,90] However, two experts with research and health systems backgrounds thought that the availability of several other treatment options for obesity minimizes the potential unmet need.[88,91] Liraglutide has good potential to improve patient outcomes as adjunctive treatment to aid in weight loss, most experts believe.[86,88,90,91] One clinical expert noted, "Weight loss, more than the specific properties of the medication, has great potential to improve health. Liraglutide also may have added benefits related to the treatment of type 2 diabetes."[86] However, another clinical expert and a research expert anticipated that liraglutide would have smaller potential to improve patient health, although they thought liraglutide has good potential to fulfill an unmet need.[87,89] One clinical expert stated, "Despite the limitations and concerns, this is a novel agent in the overall paucity of antiobesity medications. Particularly for the low BMI category that may not be amenable to surgical options, being provided with a new option that may also prevent secondary metabolic disease states or help correct obesity-associated T2DM as an adjunct benefit, it fulfills a moderate unmet need. Separately, newer similar agents brought to market will likely serve as a natural source of market competition that may help reduce the anticipated cost burden to the patient. Studies better defining the potential long-term risks (breast cancer and cardiovascular risks) need to be determined before likely seeing wider acceptance."[87] However, four experts anticipated that liraglutide is less likely to fulfill the unmet need.[86,88,90,91] One clinical expert and one research expert cited the drug's safety concerns, cost, and need for daily injections as reducing its appeal to many patients and therefore, lowering its potential to fulfill the unmet need.[86,90]

Acceptance and adoption: Experts were divided on how patients and physicians would accept liraglutide for weight loss. Three experts with research and clinical backgrounds thought that health care providers would be more accepting of the drug, because of its potential for weight loss and diabetes improvement, than patients, who might be less willing to undergo daily injections.[86,89,91] One clinical expert stated, "Providers are frequently looking for new weight loss treatments. The previous acceptance, usage, and safety profile of liraglutide will promote acceptance among providers. However, the cost may discourage some providers from recommending it to those from lower socioeconomic status groups and without insurance coverage for the medication."[86] Most experts thought that liraglutide would likely have a moderate effect on health care costs. They suggested that liraglutide's higher treatment cost compared with some other obesity drugs would be offset by its potential to reduce costs for treating obesity-related complications over the long term.[86-88,91] Two research experts thought that the drug would likely have a larger potential impact on out-of-pocket treatment costs for patients and on costs for payers that provide coverage for the drug.[89,90]

Health care delivery infrastructure and patient management: Use of liraglutide is unlikely to disrupt health care infrastructure because it is a self-injectable drug, the experts agreed. Similarly, most experts thought that the drug would have a limited disruption on the way most patients with obesity are managed. The new drug would likely be added to other drugs and counseling used by clinicians to help patients manage their conditions. Two research experts thought that the need to

train patients to administer a self-injected drug could represent a somewhat bigger change to the way patients are managed.[89,91] One clinical expert and one health systems expert anticipated that patients might more widely accept liraglutide than physicians, because of its potential health benefits.[87,88] One health systems expert noted, "Patients are likely to moderately accept liraglutide, mostly due to its success in clinical trials. Ultimately patients are more likely to be persuaded by successful clinical trials, albeit not enough evidence, and are more likely to continue trialing new interventions until the problem (obesity) is resolved."[88] One research expert expected low adoption from both patients and clinicians due to liraglutide's long-term safety concerns, cost, and need for daily injections that could deter continued use.[90]

Health disparities: Generally, experts did not expect liraglutide to substantially change health care disparities, although the cost could decrease access to the drug for less-affluent populations that might be more affected by obesity. One clinical expert noted, "There are significant health disparities issues in obesity and a great need for affordable medications to help those with obesity and from lower socioeconomic groups. Unfortunately, the projected price point makes it unlikely that it will impact the health disparities gap."[86]

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